

## REMARKS

Claims 1-46 are pending in the current application. Claims 37-46 were previously withdrawn as being directed to the non-elected invention. Claims 1-36 are therefore under examination. By way of the present Amendment, claims 1, 11, 19 and 36 are amended.

### Rejection under 35 U.S.C. § 102(b)

Claims 1, 2, 4-10, 19-26 and 36 were rejected under 35 U.S.C. § 102(b) as being anticipated by Vandekerckhove et al. (1992, Glycobiology 2:541-548). Specifically, it is the Examiner's view that Vandekerckhove et al. discloses the preparation of 2,3-sialyllactose by contacting lactose with 2,3-trans-sialidase in the presence of various sialyloligosaccharides.

In order for a rejection under 35 U.S.C. § 102(b) to be proper, each and every element of the invention must be disclosed by the cited reference. However, the Vandekerckhove reference does not teach each and every element of the instant claimed invention. Applicants' claimed invention includes complex mixtures comprising lactose, such as a dairy source. Vandekerckhove, on the other hand, discloses discreet two-saccharide, lactose-containing compositions (see paragraph entitled *Enzyme activity measurements* on page 547 of Vandekerckhove). For example, Tables I and II in the Vandekerckhove reference disclose a number of discrete reactions containing lactose and a single acceptor molecule. Table I in the reference illustrates the effect of different acceptor molecules on sialylation of lactose, using such discrete reaction mixtures as lactose and maltose, lactose and sucrose, and lactose and galactose.

On page 547 of the Vandekerckhove reference, the authors indicate that all products used in the experiments described in the paper were obtained from commercial sources. As is known to one skilled in the art, and as can be ascertained from the product catalogs of the reagent manufacturers listed by the authors, such products obtained from commercial sources are homogeneous. Further, on page 547 of Vandekerckhove, the authors indicate that all trans-sialidase activity measurements included lactose, and at

most, one additional saccharide. Therefore, Vandekerckhove discloses only compositions that necessarily include lactose, may possibly include only one saccharide in addition to lactose, and in all cases, consist of homogeneously pure components. Further still, the authors of the Vandekerckhove reference describe their reaction conditions, which include a simple buffer free of salts, proteins, lipids, and any saccharides beyond the two purified saccharides purposely included in the reaction mixture.

While not acquiescing to the Examiner's rejection, but in an attempt to expedite prosecution of the present application, Applicants have amended claims 1, 11, 19 and 36 to indicate that the to recite, "...A method of producing 2,3-sialyllactose in a dairy source...wherein said dairy source does not consist of pure lactose."

Support for the amendment of claims 1, 11, 19 and 36 to include the limitation, "wherein said dairy source does not consist of pure lactose" can be found in the as-filed specification. For example, from line 35 on page 11 through line 2 on page 12, Applicants set forth that lactose can be crystallized from whey. As known to one of ordinary skill in the art, crystallization of any particular compound is essentially a purification of that compound. As such, pure lactose is defined in the present specification as lactose existing in the absence of other substances. Another example of pure lactose according to the present invention can be found from line 16 to line 23 on page 48 in the specification. The passage on page 48 describes the isolation and purification of lactose from solution by means of crystallization.

Instant claims 1 and 36 claim the production of  $\alpha$ -2,3-sialyllactose in a dairy source. Applicants have defined a dairy source in the instant application from line 1 to line 10 of page 11 in the specification. In particular, Applicants set forth that a dairy source refers to a product of lactation in a mammal, and may comprise milk, colostrum, a composition simulating milk, and a cheese processing mixture (which includes a compilation of ingredients of dairy processing at any stage other than the cheese processing waste stream).

As is known to one of ordinary skill in the art, "milk" is a multi-component composition. The American Heritage Dictionary of the English Language (Fourth Edition, 2000) defines milk as a composition "...containing proteins, fats,

lactose, and various vitamins and minerals that is produced by the mammary glands of all mature female mammals..." The Merck Index (Twelfth Edition, 1996) defines cow's milk as a composition comprised of 3.82% fat, 3.25% protein, 4.64% lactose, and various vitamins and minerals. Milk and milk products are therefore known in the art to be comprised of multiple substances, and lactose is known to be the only sugar present in milk. Vandekerckhove does not disclose reaction mixtures containing such compositions. Therefore, amended claims 1 and 36, and any claims that depend therefrom, are not anticipated by Vandekerckhove.

Instant claims 11 and 19 claim the production of  $\alpha$ -2,3-sialyllactose in a cheese processing waste stream. Applicants have defined a cheese processing waste stream in the instant application from line 18 on page 11 through line 2 on page 12 in the specification. Applicants set forth that a cheese processing waste stream includes whole whey, demineralized whey permeate, the regeneration stream from demineralized whey permeate, whey permeate, and whey powder.

It is also known in the art that a cheese processing waste stream contains multiple components. For example, Brian et al. (U.S. Patent No. 5,575,916) disclose that whey typically comprises 5 wt. % lactose, 1 wt. % protein and about 0.5 wt % salts. Vandekerckhove does not disclose reaction mixtures containing such compositions, but rather, only compositions comprising lactose and at most, one additional saccharide. As amended, claims 11 and 19 do not recite compositions containing pure lactose. Rather, by the definition of whey given by Brian et al. and set forth above, amended claims 11 and 19 encompass compositions comprising a measurable amount of protein and/or salts in addition to lactose, if lactose is present in the composition at all. Therefore, amended claims 11 and 19, and any claims that depend therefrom, are not anticipated by Vandekerckhove.

The claims as amended herein do not encompass pure lactose. Rather, the amended claims encompass more complex mixtures of substances as set forth in the instant specification. With the exclusion of pure lactose from the amended claims, the invention encompasses dairy sources such as milk, a composition simulating milk, and a cheese processing mixture, all of which are derived from either a product of lactation in a

mammal, a substance made by such a product, or a byproduct thereof. Because milk, by chemical definition, contains no sugars other than lactose, the exclusion of “pure lactose” from the instant claimed invention necessarily requires that the claimed dairy source contains at least one of a protein, a fat, a vitamin, or a mineral in addition to lactose, if the lactose is even present in the claimed dairy source. Applicants point out that a dairy source, as claimed in the instant invention, does not require lactose, but may contain lactose, as set forth in detail throughout the specification.

Similarly, with the exclusion of pure lactose from the amended claims drawn to a “cheese processing waste stream,” such claims encompass cheese processing waste streams, including various forms of whey. Because lactose is the only sugar in whey, the exclusion of “pure lactose” from the instant claimed invention necessarily requires that the claimed cheese processing waste stream contains at least one of a protein, a fat or a mineral in addition to lactose, if the lactose is even present in the claimed cheese processing waste stream. Applicants point out that a cheese processing waste stream, as claimed in the instant invention, does not require lactose, but may contain lactose, as set forth in detail throughout the specification.

Applicants respectfully submit that the Vandekerckhove reference does not disclose each and every element of claims 1, 2, 4-10, 19-26 and 36. Applicants submit that the exclusion of pure lactose from the instant claimed invention is in compliance with MPEP 2173.05(i), which sets forth in relevant part that “Any negative limitation or exclusionary proviso must have basis in the original disclosure.” Such support for the amendments made herein has been described immediately above. Further, MPEP 2173.05(i) allows explicit exclusion of alternative elements that are positively recited in the specification. Applicants respectfully submit that the exclusion of lactose from the instant claims is in full compliance with MPEP 2173.05(i), as Applicants have specifically set forth in the as-filed specification that the complex mixtures comprising dairy sources and cheese processing waste streams of the instant invention may specifically contain lactose.

Accordingly, Applicants respectfully submit that claims 1, 2, 4-10, 19-26 and 36, as amended, are not anticipated by Vandekerckhove, and that the rejection under

35 U.S.C. § 102(b) has been overcome.

Rejection under 35 U.S.C. § 103(a)

Claims 1-35 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vandekerckhove et al. in view of Brian et al. (U.S. Patent No. 5,575,916, issued November 19, 1996; the “916 patent”) and Ito et al. (U.S. Patent No. 5,409,817, issued April 25, 1995; the “817 patent”). Specifically, it is the Examiner’s view that it would have been obvious for one of skill in the art to practice the present invention when considering Brian’s disclosure of the presence of 2,3-trans-sialidase substrates in dairy products and Ito’s disclosure of the utility of 2,3-sialyllactose produced by enzymatic action on sialyl Lewis x, in light of the disclosure of Vandekerckhove (described above in response to the 35 U.S.C. § 102(b) rejection). Applicants respectfully submit that claims 1-35 are not obvious for the reasons set forth below.

In order for the rejection under 35 U.S.C. § 103(a) to be proper, the Examiner establish a *prima facie* case of obviousness. More specifically, it must be shown that there is some suggestion or motivation to combine the cited references, that the prior art provides one of ordinary skill in the art with a reasonable expectation of success, and that the combination of the art teaches or suggests each and every element of the rejected claims.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The Examiner argues that Vandekerckhove teaches the preparation of  $\alpha$ -2,3-sialyllactose by contacting lactose with  $\alpha$ -2,3-trans-sialidase “in the presence of various sialyloligosaccharides.” Continuing, the Examiner also argues that Brian disclose that dairy products, including cheese processing waste, contain sialyloligosaccharides which are substrates for  $\alpha$ -2,3-trans-sialidase. It is the Examiner’s view that one of skill in the art, when armed with the Vandekerckhove and Brian references, would have deemed it obvious to prepare sialyloligosaccharides according to Applicant’s claimed invention. Applicants respectfully disagree for the following reasons.

Applicants respectfully point out, as set forth above in the response to the rejection under 35 U.S.C. § 102(b), that Vandekerckhove teaches only  $\alpha$ -2,3-trans-sialidase activity in certain discrete reactions containing lactose and one additional saccharide, not in a mixture of components as is disclosed in the Applicants invention, such mixtures including multiple proteins, lipids and minerals. As set forth above, Vandekerckhove teaches only compositions including a minimal number of purified components. Further, Vandekerckhove teaches compositions that necessarily include lactose, compositions that may possibly include only one saccharide in addition to lactose, and in all cases, compositions that consist of homogeneously pure components.

Regarding the Brian reference, as pointed out by the Examiner, the Brian reference discloses only the presence of sialyloligosaccharides in dairy products and cheese processing waste streams. In fact, Brian specifically teaches the advantages of and claims methods of purifying sialyloligosaccharides away from the dairy sources and cheese processing waste streams. Brian teaches that the existence of excess cheese processing waste is troublesome, and proposes to remedy the situation by processing the waste (i.e., separating and purifying the components of the waste) (see lines 45-52 in column 2 of the Brian patent). Because Brian teaches the purification of sialyloligosaccharides and Vandekerckhove teaches trans-sialidase activity only under simple reaction conditions containing only purified oligosaccharide components in addition to the trans-sialidase, Applicants respectfully submit that it would not be obvious

to one of skill in the art to combine Vandekerckhove and Brian to arrive at Applicant's invention.

In fact, the combination of Vandekerckhove and Brian teaches away from Applicants' claimed invention, because neither Vandekerckhove nor Brian, when taken alone or in combination, teaches or suggests that adding a trans-sialidase to a crude or impure reaction mixture would result in the successful production of sialyloligosaccharides. Vandekerckhove actually teaches that numerous saccharides, such as lactobionic acid and N-acetyl-lactosamine, **inhibit** the production of sialyllactose (see Table I in the Vandekerckhove article), and the authors of the article state that sialylation of lactose decreases in the presence of disaccharides containing  $\beta$ -linked, but not  $\alpha$ -linked terminal galactopyranosyl residues (see Results on page 541 of the Vandekerckhove article). Therefore, Applicants respectfully submit that one of skill in the art, when armed with the teachings of Vandekerckhove and Brian, would, at most, only be motivated to practice trans-sialidation of purified saccharides. Further, one of skill in the art, when armed with the teachings of Vandekerckhove and Brian, would, at most, have a reasonable expectation of success in sialylating purified saccharides.

As is known to one of skill in the art of enzymology, an enzyme is highly sensitive to its reaction milieu. As described in detail above, Vandekerckhove teaches trans-sialidase activity with purified starting materials in reaction mixtures containing very few reactants under tightly controlled reaction conditions. In the instant application, Applicants' claimed invention does not utilize purified starting materials, but rather, the claimed invention utilizes dairy sources and cheese processing waste streams. As defined in the instant specification and set forth in detail above, Applicants' starting materials contain one or more of proteins, lipids and minerals, and may or may not contain lactose. One of skill in the art would know that the presence of extraneous proteins, salts, minerals, and/or lipids in a reaction mixture can significantly alter enzymatic activity. Applicants submit that, because Vandekerckhove also teaches that many saccharides inhibit trans-sialidase activity, one of skill in the art of enzymology viewing Brian in light of Vandekerckhove would **not** be motivated to practice the instant claimed invention, because there is no teaching or suggestion, nor a reasonable expectation of success to add

a trans-sialidase to a complex, crude or impure reaction mixture. Accordingly, Applicants respectfully submit that rejection under 35 U.S.C. § 103(a) is improper and request withdrawal of the rejection.

It is also the Examiner's view that Vandekerckhove and Brian, taken in light of Ito, would motivate one of skill in the art to practice the instant claimed invention, based on the known utility of the sialyloligosaccharide "sialyl Lewis x." Applicants respectfully submit that, in view of the above-described amendments to the claims, and because neither Vandekerckhove nor Brian teaches or suggest the use of an  $\alpha$ -2,3-trans-sialidase under conditions sufficient to enrich the content of sialyloligosaccharides in a composition such as a dairy source or a cheese processing waste stream, the Ito reference would not motivate one of skill in the art to practice the instant invention. The known utility of sialylated oligosaccharides, such as sialyl Lewis x, is by itself not enough to motivate one skilled in the art to practice the instant claimed invention. Applicants respectfully submit that the Examiner's application of the Ito reference in this way is improper hindsight reasoning, as the Examiner's claim that the knowledge of the utility of sialyl Lewis x would motivate one skilled in the art to contact, for example, a cheese processing waste stream with an  $\alpha$ -2,3-trans-sialidase under conditions sufficient to enrich the content of sialyloligosaccharides in the waste stream, is based on knowledge disclosed for the first time in the present application. For example, Applicants have shown for the first time that  $\alpha$ -2,3-trans-sialidase can be successfully used in a complex dairy source to produce sialyloligosaccharides, such as sialyllactose. Accordingly, Applicants submit that rejection under 35 U.S.C. § 103(a) is improper and request withdrawal of the rejection.

Summary

The amendments made herein are supported in the as-filed specification, and as such, no new matter has been added by way of the present amendment. Applicants respectfully submit that each and every rejection or objection set forth by the Examiner has either been overcome or is now inapplicable, and that the instant application is in full condition for allowance. Favorable examination of the claims on the merits is respectfully requested.

Respectfully submitted,  
MARC PELLETIER, ET AL.

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By: Kathryn Doyle  
KATHRYN DOYLE, Ph.D., J.D.  
Registration No. 36,317  
MORGAN, LEWIS & BOCKIUS, L.L.P.  
1701 Market Street  
Philadelphia, PA 19103-2921  
Telephone No.: 215-963-5000  
**Direct Telephone: 215-963-4723**  
Facsimile: (215) 963-5299  
E-Mail: kdoyle@morganlewis.com

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